acceptor molecule" and b) a catalytic domain of an accessory enzyme "that catalyzes the formation of the nucleotide sugar." Support for this amendment is provided throughout the specification, for example, at page 3, line 21, to page 5, line 15. Claim 9 is amended to correct for minor editorial error and to more clearly define the recited group of accessory enzymes. Claim 23 is amended to more clearly define that the recited catalytic domains are "joined" by a peptide linker. Support for this amendment is provided, for example, at page 26, line 26, to page 27 line 8 of the specification. Claim 26 is amended to correct for minor editorial error, replacing "a" nucleic acid of claim 1 with "the" nucleic acid of claim 1. Claims 27 and 33 are amended to depend from claim 26 which is directed to an expression vector comprising the nucleic acid of claim 1. Support for this amendment is provided throughout the specification, for example, at page 32, line 27, to page 35 line 17. Newly added claim 36, depends from claim 1, and covers a pyrophosphorylase as the accessory enzyme. Support for this claim is provided, for example, at page 18, line 29, to page 22, line 27 of the specification. Therefore, no new matter has been added.

In the following remarks, Applicants address each of the rejections set forth in the Office Action dated February 26, 2001.

I. Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-27 and 33-35 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in a way to enable one skilled in the art to make and/or use the invention. In addition, claims 1-14, 16-27, and 33-35 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter that is not sufficiently described in the specification to convey to one skilled in the art that the inventors possessed the claimed invention at the time the application was filed. Applicants disagree with these allegations and traverse in part and overcome in part the rejections under this section.

Claims 1-27 and 33-35

With respect to claims 1-27 and 33-35, the Examiner points out that the specification is enabling for a polynucleotide that encodes a fusion protein comprising a specifically identified glycosyltransferase and a specifically identified accessory enzyme. However, the Examiner alleges that the specification is not enabling for a polynucleotide that encodes a fusion protein comprising any glycosyltransferase and any accessory enzyme that catalyzes a step in the formation of a nucleotide sugar that is a saccharide donor for a glycosyltransferase. Specifically, it is alleged that without a specific accessory enzyme, one

of skill in the art would not know how to make and use the glycosyltransferase and vice versa. In addition, the claims allegedly encompass any enzyme involved in any step of biosynthesis of a nucleotide or a sugar. Thus, the Examiner further alleges that undue experimentation would be required to enable the full scope of the claims based upon the instant disclosure.

Applicants disagree with the Examiner's allegations and assert that one skilled in the art would know how to make and use the recited glycosyltransferase and accessory enzyme, because the identity and function of these enzymes in the biosynthetic pathway for catalyzing the transfer of a saccharide, from a saccharide donor to an acceptor molecule, are well-established and highly specific. These enzymes include accessory enzymes that catalyze the formation of the nucleotide sugar of a saccharide donor, and the glycosyltransferases that catalyze the transfer of the saccharide from a saccharide donor comprising the nucleotide sugar. In particular, for any glycosidic bond, there exists a specific glycosyltransferase and a specific set of accessory enzymes that result in the highly stereo- and regioselective formation of this bond. Moreover, it is well known in the art that glycosyltransferases use a specific and defined group of activated nucleotide sugars that serve as donor substrates. Such activated sugars consist of uridine, guanosine, and cytidine monophosphate or diphosphate derivatives of the sugars in which the nucleoside monophosphate or diphosphate serves as a leaving group. For example, sialyltransferases catalyze the transfer of sialic acid from CMP-sialic acid; galactosyltransferases catalyze the transfer of galactose from UDP-galactose; fucosyltransferases catalyze the transfer of fucose from GDP-fucose; and N-acetylglucosaminyltransferases catalyze the transfer of N-acetylglucosamine from UDP-N-acetylglucosamine. Thus, one skilled in the art would know how to identify and select an accessory enzyme that catalyzes the formation of the nucleotide sugar of the donor substrate utilized by the recited glycosyltransferase, without undue experimentation. Likewise, one skilled in the art would know how to identify and select a glycosyltransferase that catalyzes the transfer of a saccharide from a saccharide donor comprising the nucleotide sugar formed by the recited accessory enzyme, without undue experimentation. See, *e.g.*, Guo *et al.*, *Applied Biochem. and Biotech.* (1997) 68,1-20 (attached). Also see, *e.g.*, the specification, page 12, line 8, to page 23, line 16.

For example, one skilled in the art would know that galactosyltransferases generally use as a galactose donor the activated nucleotide sugar UDP-Gal. Moreover, the accessory enzymes involved in the biosynthetic pathway that results in the formation of

UDP-Gal are known. For example, glucokinase (EC 2.7.1.12) catalyzes the phosphorylation of glucose to Glc-6-P; phosphoglucomutase (EC 5.4.2.2) catalyzes the conversion of Glc-6-P to Glc-1-P; UDP-glucose pyrophosphorylase (EC 2.7.7.9) catalyzes the conversion of Glc-1-P to UDP-Glc; and finally, UDP-Glc 4'-epimerase (EC 5.1.3.2) catalyzes the conversion of UDP-Glc to UDP-Gal. See, *e.g.*, Guo *et al.*, *Applied Biochem. and Biotech.* (1997) **68**,7-8 (attached). See also, *e.g.*, page 13, line 28, to page 14, line 13. Thus, one skilled in the art would know how to make and use the recited glycosyltransferases and accessory enzymes, because the identity and function of these enzymes, in the biosynthetic pathway for catalyzing the transfer of a saccharide from a donor substrate to an acceptor molecule and for forming the nucleotide sugar of the donor saccharide, are well-established. Moreover, the enzymatic activity of these enzymes is highly specific. Undue experimentation would not be required to make and use the recited glycosyltransferase and accessory enzyme.

To more clearly define the claimed invention, claim 1, and the claims depending therefrom, are amended to recite a fusion protein comprising 1) a catalytic domain of a glycosyltransferase that catalyzes the transfer of a saccharide, from a saccharide donor comprising a nucleotide sugar, to an acceptor molecule; and 2) a catalytic domain of an accessory enzyme that catalyzes the formation of the nucleotide sugar. This amendment is consistent with Applicants' assertions that it is well known in the art that glycosyltransferases have a specific and defined group of activated nucleotide sugars that serve as donor substrates; and that the accessory enzymes and the biosynthetic pathway that catalyze the formation of these particular nucleotide sugars are well-established and highly specific. Thus, one skilled in the art would know how to make and use the recited glycosyltransferase and accessory enzyme, without undue experimentation.

Further, claim 4 is cancelled to expedite prosecution. Therefore, the rejection of claim 4 is obviated.

In view of the above arguments and amendments, Applicants respectfully request that the rejection be withdrawn.

Claims 1-14, 16-27, and 33-35

The Examiner points out that claims 1-14, 16-27, and 33-35 are drawn to DNA encoding a glycosyltransferase and an accessory enzyme that catalyzes a step in the formation of a nucleotide sugar. However, the Examiner alleges that the specification provides no DNA sequences or sufficient methods to obtain the claimed DNA. Moreover, it

is alleged that there is no correlation that relates the functional characteristics of the DNA to the structure of the DNA.

Applicants disagree with the Examiner's allegations and argue that the specification is replete with description teaching DNA sequences encoding glycosyltransferases and accessory enzymes, the structure and function of the DNA, and methods for obtaining the DNA (see, *e.g.*, the specification, page 11, line 26, to page 27, line 12). Likewise, the Examples demonstrate a clear correlation between the structure and function of the DNA, and teach DNA sequences and methods for obtaining the DNA (see, *e.g.*, the specification, page 38, line 12, to page 52, line 6).

For example, the specification describes the structure and function of DNAs encoding glycosyltransferases and accessory enzymes (see, *e.g.*, the specification, page 12, line 8, to page 23, line 16.), and describes how to obtain and clone DNA encoding such glycosyltransferases and accessory enzymes (see, *e.g.*, the specification, page 23, line 17, to page 27, line 12). Moreover, the specification describes DNA sequences encoding specific protein domains of glycosyltransferases (*e.g.*, catalytic domain, cytoplasmic domain, signal-anchor domain, and stem region) and of accessory enzymes, and the function of the encoded protein domains (see, *e.g.*, the specification, page 12, lines 18 to 27; and page 23, line 17, to page 27, line 12).

Further, Example 1 describes the construction and expression of a DNA that encodes a CMP-Neu5Ac synthetase/α2,3-sialyltransferase fusion protein that has both CMP-Neu5Ac synthetase activity and α2,3-sialyltransferase activity (see the specification, page 38, line 12, to page 49, line 8). Similarly, Example 2 describes the construction and expression of a DNA that encodes a UDP-glucose epimerase/β-1,4-galactosyltransferase fusion protein that has both UDP-glucose epimerase and β-1,4-galactosyltransferase activity (see the specification, page 49, line 9, to page 52, line 6). The precise identity or structure of the DNA used to construct the DNA encoding each fusion protein is described in the Examples. Moreover, the results described in Example 1 demonstrate that the CMP-Neu5Ac synthetase/α-2,3-sialyltransferase fusion protein was expressed at high levels and had both of the encoded enzymatic activities (*i.e.*, CMP-Neu5Ac synthetase and α-2,3-sialyltransferase activity); and the results described in Example 2 demonstrate that the UDP glucose epimerase/β-1,4-galactosyltransferase fusion protein was expressed at high levels and had both of the encoded enzymatic activities (*i.e.*, UDP glucose epimerase and β-1,4-

galactosyltransferase activity). Therefore, the results described in Examples 1 and 2 clearly demonstrate a clear correlation between the structure and function of the DNA.

Further, claim 4 is cancelled to expedite prosecution. Therefore, the rejection of claim 4 is obviated.

In view of the above arguments, Applicants respectfully request that the rejections under § 112, first paragraph, be withdrawn.

Rejections Under §112, Second Paragraph

Claims 4, 9, 33, and 35 are rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite. Applicants obviate the rejection of claim 4; overcome the rejection of claim 9; and respectfully traverse the rejection of claims 33 and 35, under this section.

Claim 4

With respect to claim 4, it is allegedly unclear how a catalytic domain of a glycosyltransferase would include domains or regions not involved in catalysis, for example, the cytoplasmic domain, signal-anchor domain, and stem region. As stated above, in order to expedite prosecution, claim 4 is cancelled.

Claim 9

With respect to claim 9, it is allegedly unclear if the GDP mannose enzymes are grouped as one group of accessory enzymes or as separate members of a Markush Group. In order to more clearly define the claimed invention, claim 9 is amended to insert a semicolon after each recited GDP-mannose and to delete any extraneous punctuation and connectives.

Claims 33 and 35

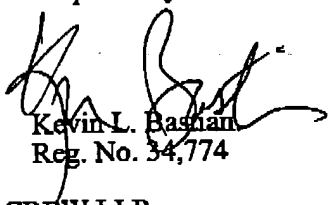
With respect to claims 33 and 35, the claims are allegedly incomplete because they are missing the essential step of isolating the fusion polypeptide. Applicants disagree with this allegation and provide the following arguments. Applicants assert that claims 33 and 35 are directed to a method of producing a fusion polypeptide and that this method is complete once the fusion polypeptide is produced. For example, the fusion polypeptide may be expressed and secreted by the host cell and used in this form without a further step of isolating the expressed and/or secreted polypeptide. Such use is described, for example, at page 33, lines 18-29 of the specification.

In view of the above arguments and amendments, Applicants respectfully request that the rejections under § 112, second paragraph, be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe that all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance is respectfully requested.

Respectfully submitted,



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VERSION OF PENDING CLAIMS WITH MARKINGS TO SHOW CHANGES MADE

1. **(once amended)** [A nucleic acid which comprises a polynucleotide] An isolated nucleic acid that encodes a fusion polypeptide, wherein the fusion polypeptide comprises:

a) a catalytic domain of a glycosyltransferase that catalyzes the transfer of a saccharide, from a saccharide donor comprising a nucleotide sugar, to an acceptor molecule; and

b) a catalytic domain of an accessory enzyme [which catalyzes a step in the formation of a nucleotide sugar which is a saccharide donor for the glycosyltransferase] that catalyzes the formation of the nucleotide sugar.

2. The nucleic acid of claim 1, wherein the glycosyltransferase is a eukaryotic glycosyltransferase.

3. The nucleic acid of claim 1, wherein the accessory enzyme is a eukaryotic accessory enzyme.

4. **(cancelled)** The method of claim 2, wherein the catalytic domain of the glycosyltransferase substantially lacks one or more of a cytoplasmic domain, a signal-anchor domain, and a stem region of the glycosyltransferase.

5. The nucleic acid of claim 1, wherein the glycosyltransferase is a prokaryotic glycosyltransferase.

6. The nucleic acid of claim 1, wherein the accessory enzyme is a prokaryotic accessory enzyme.

7. The nucleic acid of claim 1, wherein the fusion polypeptide further comprises a catalytic domain of a second accessory enzyme.

8. The nucleic acid of claim 1, wherein the glycosyltransferase is selected from the group consisting of sialyltransferases, *N*-acetylglucosaminyltransferases, *N*-acetylgalactosaminyltransferases, fucosyltransferases, galactosyltransferases, glucosyltransferases, glucuronosyltransferases, xylosyltransferases, and mannosyltransferases.

9. **(once amended)** The nucleic acid of claim 1, wherein the accessory enzyme is selected from the group consisting of:

a GDP-mannose dehydratase[,];

a GDP-mannose 3,5-epimerase[, and];

a GDP-mannose 4-reductase;

a UDP-glucose 4' epimerase;

a UDP-GalNAc 4' epimerase;

a CMP-sialic acid synthetase;

a neuraminic acid aldolase;

an *N*-acetylglucosamine 2' epimerase;

a phosphate kinase selected from the group consisting of a pyruvate kinase, a myokinase, a creatine phosphate kinase, an acetyl phosphate kinase, and a polyphosphate kinase; and

a pyrophosphorylase selected from the group consisting of a UDP-Glc pyrophosphorylase, a UDP-Gal pyrophosphorylase, a UDP-GalNAc pyrophosphorylase, a GDP-mannose pyrophosphorylase, a GDP-fucose pyrophosphorylase, and a UDP-GlcNAc pyrophosphorylase.

10. The nucleic acid of claim 1, wherein the nucleotide sugar is selected from the group consisting of GDP-Man, UDP-Glc, UDP-Gal, UDP-GlcNAc, UDP-GalNAc, CMP-sialic acid, GDP-Fuc, and UDP-xylose.

11. The nucleic acid of claim 1, wherein the glycosyltransferase is a sialyltransferase and the nucleotide sugar is CMP-sialic acid.

12. The nucleic acid of claim 11, wherein the accessory enzyme is a CMP-sialic acid synthetase.

13. The nucleic acid of claim 11, wherein the accessory enzyme is a neuraminic acid aldolase or an *N*-acetylglucosamine 2' epimerase.

14. The nucleic acid of claim 1, wherein the glycosyltransferase is a galactosyltransferase and the nucleotide sugar is UDP-galactose.

15. The nucleic acid of claim 14, wherein the accessory enzyme is a UDP-glucose 4' epimerase.

16. The nucleic acid of claim 1, wherein the glycosyltransferase is a fucosyltransferase and the nucleotide sugar is GDP-fucose.

17. The nucleic acid of claim 16, wherein the accessory enzyme is selected from the group consisting of a GDP-mannose dehydratase, a GDP-mannose 3,5-epimerase, a GDP-fucose pyrophosphorylase, and a GDP-mannose 4-reductase.

18. The nucleic acid of claim 1, wherein the glycosyltransferase is an *N*-acetylgalactosaminyltransferase and the nucleotide sugar is UDP-GalNAc.

19. The nucleic acid of claim 18, wherein the accessory enzyme is a UDP-GalNAc 4' epimerase.

20. The nucleic acid of claim 1, wherein the glycosyltransferase is an *N*-acetylglucosaminyltransferase and the nucleotide sugar is UDP-GlcNAc.

21. The nucleic acid of claim 20, wherein the accessory enzyme is a UDP-GalNAc 4' epimerase.

22. The nucleic acid of claim 1, wherein the glycosyltransferase is a mannosyltransferase and the nucleotide sugar is GDP-Man.

23. **(once amended)** The nucleic acid of claim 1, wherein [the fusion polypeptide further comprises a linker peptide between the glycosyltransferase catalytic domain and the accessory enzyme catalytic domain] the catalytic domain of the glycosyltransferase and the catalytic domain of the accessory enzyme are joined by a peptide linker.

24. The nucleic acid of claim 1, wherein the nucleic acid further comprises a polynucleotide that encodes a signal sequence which is linked to the fusion polypeptide.

25. The nucleic acid of claim 1, wherein the nucleic acid further comprises a polynucleotide that encodes a molecular tag which is linked to the fusion polypeptide.

26. **(once amended)** An expression vector which comprises [a] the nucleic acid of claim 1.

27. **(once amended)** A host cell which comprises [a nucleic acid of claim 1] the expression vector of claim 26.

28. **(withdrawn and cancelled)** A fusion polypeptide encoded by a nucleic acid of claim 1.

29. **(withdrawn and cancelled)** A fusion polypeptide that comprises:

a) a catalytic domain of a glycosyltransferase; and

b) a catalytic domain of an accessory enzyme which catalyzes a step in the formation of a nucleotide sugar which is a donor for the glycosyltransferase.

30. **(withdrawn and cancelled)** The fusion polypeptide of claim 29, wherein the catalytic domain of the glycosyltransferase is joined to the carboxy terminus of the accessory enzyme catalytic domain.

31. **(withdrawn and cancelled)** The fusion polypeptide of claim 29, wherein the glycosyltransferase is a galactosyltransferase and the accessory enzyme is a UDP-glucose 4' epimerase.

32. **(withdrawn and cancelled)** The fusion polypeptide of claim 29, wherein the glycosyltransferase is a sialyltransferase and the accessory enzyme is a CMP-sialic acid synthetase.

33. **(once amended)** A method of producing a fusion polypeptide [that comprises:

a) a catalytic domain of a glycosyltransferase; and

b) a catalytic domain of an accessory enzyme which catalyzes a step in the formation of a nucleotide sugar which is a donor for the glycosyltransferase;

wherein the method comprises introducing a nucleic acid that encodes the fusion polypeptide into a host cell to produce a transformed host cell; and culturing the transformed host cell under conditions appropriate for expressing the fusion polypeptide], the method comprising:

a) introducing into a host cell the expression vector of claim 26, under conditions where the host cell is transformed with the expression vector; and

b) culturing the transformed host cell under conditions where the fusion polypeptide is expressed in the transformed host cell.

34. **(once amended)** The method of claim 33[, wherein the fusion polypeptide is purified following its expression] further comprising a step of purifying the expressed fusion polypeptide.

35. **(once amended)** The method of claim 33[, wherein the host cell is permeabilized following expression of the fusion polypeptide] further comprising a step of permeabilizing the host cell expressing the fusion polypeptide.

36. **(newly added)** The nucleic acid of claim 1, wherein the accessory enzyme is a pyrophosphorylase.

PENDING CLAIMS

1. **(once amended)** An isolated nucleic acid that encodes a fusion polypeptide, wherein the fusion polypeptide comprises:

a) a catalytic domain of a glycosyltransferase that catalyzes the transfer of a saccharide, from a saccharide donor comprising a nucleotide sugar, to an acceptor molecule; and

b) a catalytic domain of an accessory enzyme that catalyzes the formation of the nucleotide sugar.

2. The nucleic acid of claim 1, wherein the glycosyltransferase is a eukaryotic glycosyltransferase.

3. The nucleic acid of claim 1, wherein the accessory enzyme is a eukaryotic accessory enzyme.

5. The nucleic acid of claim 1, wherein the glycosyltransferase is a prokaryotic glycosyltransferase.

6. The nucleic acid of claim 1, wherein the accessory enzyme is a prokaryotic accessory enzyme.

7. The nucleic acid of claim 1, wherein the fusion polypeptide further comprises a catalytic domain of a second accessory enzyme.

8. The nucleic acid of claim 1, wherein the glycosyltransferase is selected from the group consisting of sialyltransferases, *N*-acetylglucosaminyltransferases, *N*-acetylgalactosaminyltransferases, fucosyltransferases, galactosyltransferases, glucosyltransferases, glucuronosyltransferases, xylosyltransferases, and mannosyltransferases.

9. **(once amended)** The nucleic acid of claim 1, wherein the accessory enzyme is selected from the group consisting of:

a GDP-mannose dehydratase;

a GDP-mannose 3,5-epimerase;

a GDP-mannose 4-reductase;

a UDP-glucose 4' epimerase;

a UDP-GalNAc 4' epimerase;

a CMP-sialic acid synthetase;

a neuraminic acid aldolase;

an *N*-acetylglucosamine 2' epimerase;

a phosphate kinase selected from the group consisting of a pyruvate kinase, a myokinase, a creatine phosphate kinase, an acetyl phosphate kinase, and a polyphosphate kinase; and

a pyrophosphorylase selected from the group consisting of a UDP-Glc pyrophosphorylase, a UDP-Gal pyrophosphorylase, a UDP-GalNAc pyrophosphorylase, a GDP-mannose pyrophosphorylase, a GDP-fucose pyrophosphorylase, and a UDP-GlcNAc pyrophosphorylase.

10. The nucleic acid of claim **1**, wherein the nucleotide sugar is selected from the group consisting of GDP-Man, UDP-Glc, UDP-Gal, UDP-GlcNAc, UDP-GalNAc, CMP-sialic acid, GDP-Fuc, and UDP-xylose.

11. The nucleic acid of claim **1**, wherein the glycosyltransferase is a sialyltransferase and the nucleotide sugar is CMP-sialic acid.

12. The nucleic acid of claim **11**, wherein the accessory enzyme is a CMP-sialic acid synthetase.

13. The nucleic acid of claim **11**, wherein the accessory enzyme is a neuraminic acid aldolase or an *N*-acetylglucosamine 2' epimerase.

14. The nucleic acid of claim **1**, wherein the glycosyltransferase is a galactosyltransferase and the nucleotide sugar is UDP-galactose.

15. The nucleic acid of claim **14**, wherein the accessory enzyme is a UDP-glucose 4' epimerase.

16. The nucleic acid of claim **1**, wherein the glycosyltransferase is a fucosyltransferase and the nucleotide sugar is GDP-fucose.

17. The nucleic acid of claim **16**, wherein the accessory enzyme is selected from the group consisting of a GDP-mannose dehydratase, a GDP-mannose 3,5-epimerase, a GDP-fucose pyrophosphorylase, and a GDP-mannose 4-reductase.

18. The nucleic acid of claim **1**, wherein the glycosyltransferase is an *N*-acetylgalactosaminyltransferase and the nucleotide sugar is UDP-GalNAc.

19. The nucleic acid of claim **18**, wherein the accessory enzyme is a UDP-GalNAc 4' epimerase.

20. The nucleic acid of claim 1, wherein the glycosyltransferase is an *N*-acetylglucosaminyltransferase and the nucleotide sugar is UDP-GlcNAc.

21. The nucleic acid of claim 20, wherein the accessory enzyme is a UDP-GalNAc 4' epimerase.

22. The nucleic acid of claim 1, wherein the glycosyltransferase is a mannosyltransferase and the nucleotide sugar is GDP-Man.

23. **(once amended)** The nucleic acid of claim 1, wherein the catalytic domain of the glycosyltransferase and the catalytic domain of the accessory enzyme are joined by a peptide linker.

24. The nucleic acid of claim 1, wherein the nucleic acid further comprises a polynucleotide that encodes a signal sequence which is linked to the fusion polypeptide.

25. The nucleic acid of claim 1, wherein the nucleic acid further comprises a polynucleotide that encodes a molecular tag which is linked to the fusion polypeptide.

26. **(once amended)** An expression vector which comprises the nucleic acid of claim 1.

27. **(once amended)** A host cell which comprises the expression vector of claim 26.

33. **(once amended)** A method of producing a fusion polypeptide, the method comprising:

a) introducing into a host cell the expression vector of claim 26, under conditions where the host cell is transformed with the expression vector; and

b) culturing the transformed host cell under conditions where the fusion polypeptide is expressed in the transformed host cell.

34. **(once amended)** The method of claim 33 further comprising a step of purifying the expressed fusion polypeptide.

35. **(once amended)** The method of claim 33 further comprising a step of permeabilizing the host cell expressing the fusion polypeptide.

36. **(newly added)** The nucleic acid of claim 1, wherein the accessory enzyme is a pyrophosphorylase.